RESEARCH PROPOSAL

Synthesis and Application of New Thiourea Based Organocatalysts

For registration to the degree of Doctor of Philosophy

IN THE FACULTY OF SCIENCE

THE IIS (Deemed to be University), JAIPUR

Submitted by

Nivedita Sharma

ICG/2018/26405

Under the supervision of

Supervisor

Prof. Raj K Bansal

Co-Supervisor

Dr. Raakhi Gupta

Department of Chemistry

May, 2019

Synthesis and Application of New Thiourea Based Organocatalysts

Introduction

Organocatalysts are non-metallic, eco-friendly catalysts that work under mild reaction conditions. Over the last two decades, this field has witnessed a remarkable growth. A number of organic reactions, such as Diels-Alder reaction, Michael reaction, Mannich reaction, Shi epoxidation and many more could be mediated successfully by organocatalysts accompanied by dramatic improvement in the rate and selectivity.[1]

Properties of a good organocatalyst:

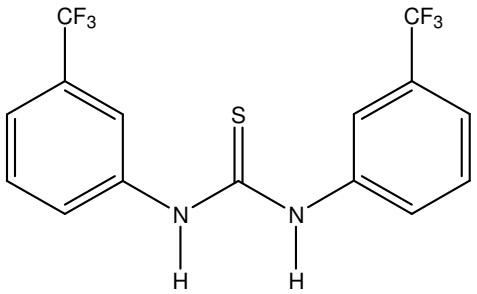
- ✓ Hydrogen binding catalyst should efficiently bind with TS and should avoid binding with starting material, product or itself.
- ✓ Presence of electron-withdrawing group e.g. CF_3 moiety plays an important role in limiting the self-association ability of the catalyst. And it also increases reaction rate due to inductive effect.
- ✓ Should possess high acidic nature[2] [facilitates Lewis base binding] and
- ✓ Should have poor H-bond acceptor ability [which limits self-association].

For asymmetric synthesis, a wide range of organocatalysts has been developed using biomolecules, such as proline, phenylalanine, thiourea derivatives, urea derivatives or imidazolidinone derivatives.

In many cases, hydrogen bonding interactions play a vital role and increase the efficacy of organocatalysts. Some examples of these types of catalysts are thiourea and urea derivatives, diols and amidinium cations. Initially, urea and thiourea based organocatalyst were developed in 1980's. The use of urea derivative as organocatalyst was often accompanied by polymerization and other side products. This difficulty was overcome by the use of thiourea derivatives as organocatalyst. As hydrogen bond catalyst, thiourea derivatives showed improved catalyzing effect without side reactions.[3]

Ever since the synthesis of the first thiourea catalyst reported in literature, many research groups were attracted to develop new organocatalysts having some specific features. Newer approaches are being developed for its synthesis and its application.

Advent of the thiourea based organocatalyst:



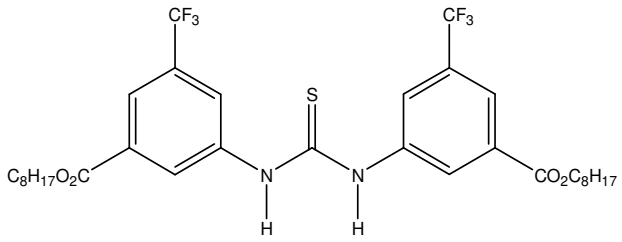
Thiourea derivatives are more preferred catalyst as compared to urea derivatives in organic reactions (such as Diels-Alder) because thioureas derivatives:

- are soluble in a wide range of solvents.[4]
- possess great ability as hydrogen-bond donor to carbonyl groups leading to effective substrate binding.
- avoid self-association due to low electronegativity of sulfur.[5]
- are expected to make better catalyst than urea based on pKa values (thiourea = 21.0; urea = 26.9).[2]

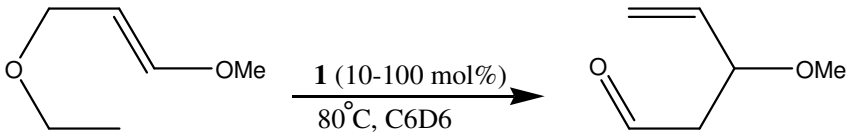
The use of thiourea derivatives has revolutionized the organic synthesis and has become a fascinating subject of interest for catalyst design (**1**).[6]

Review of literature:

Since 1990's thiourea derivatives were also shown to hold promise as hydrogen bonding catalyst.[7] In 1994, first thiourea based organocatalyst (**1**) was developed for comparative study with its urea derivative on chemical reaction such as Claisen rearrangement.



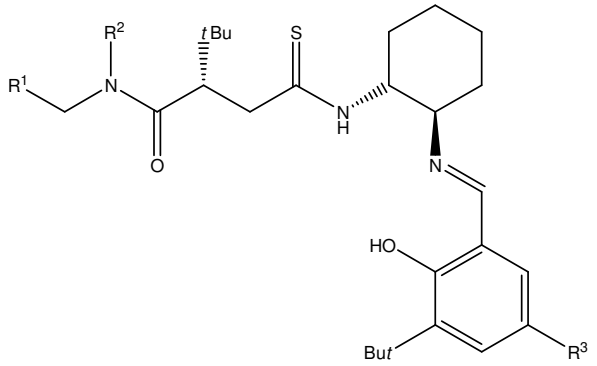
1



Scheme 1: Diiaryl(thio)urea catalysis of the Claisen rearrangement.[4]

Note: Later Schreiner has established that diarylthiourea can catalyse Diels-Alder reaction.[8,9]

In 1998, chiral thiourea derivatives were synthesized by using enantiopure chiral building blocks bearing primary amino functionality.



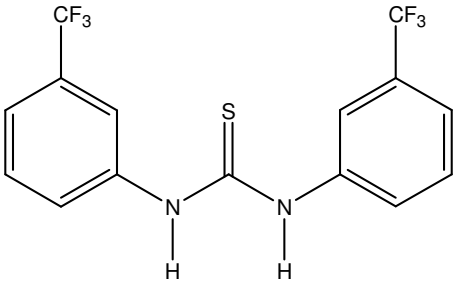
2

These chiral catalysts **2** provide high stability and conformational rigidity.[10] Chiral catalysts turn up with useful features like:

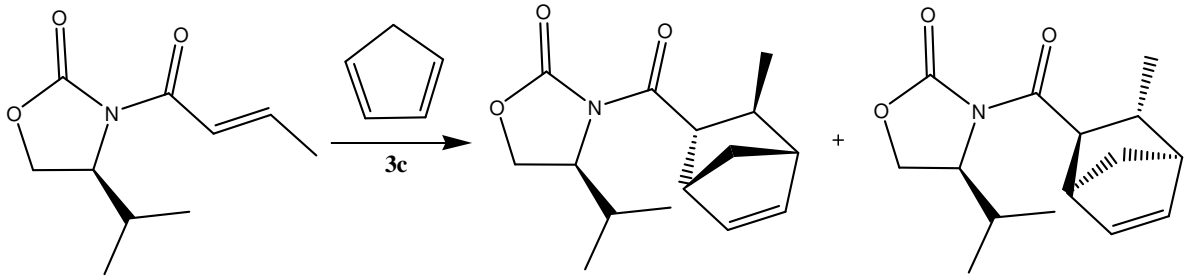
- Versatile
- Functional group tolerant and
- For the wide range of asymmetric synthesis, these catalysts can be easily prepared and modified.

A combination of subsequent parallel library and conventional linear optimization studies resulted in the identification of **2** as an efficient and highly enantioselective catalyst for the Strecker reaction.[11]

For limiting the self-association ability of catalyst, Lewis basic ester linkage was removed from **1** and new catalyst **3** was designed with retention of the strong electron withdrawing CF_3 moiety.[12] In 2002, Schreiner has established that catalyst **3** showed efficient catalysis of Diels-Alder reaction between cyclopentadiene and α-β unsaturated carbonyl compound.[8]



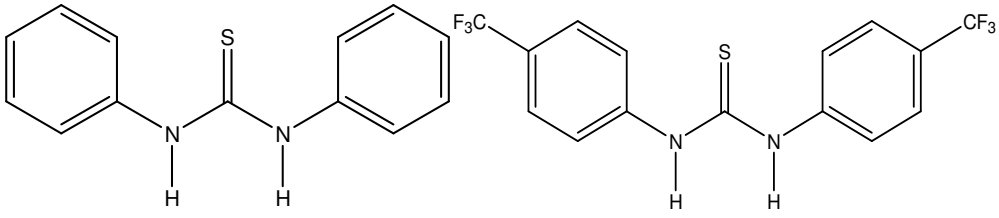
3c



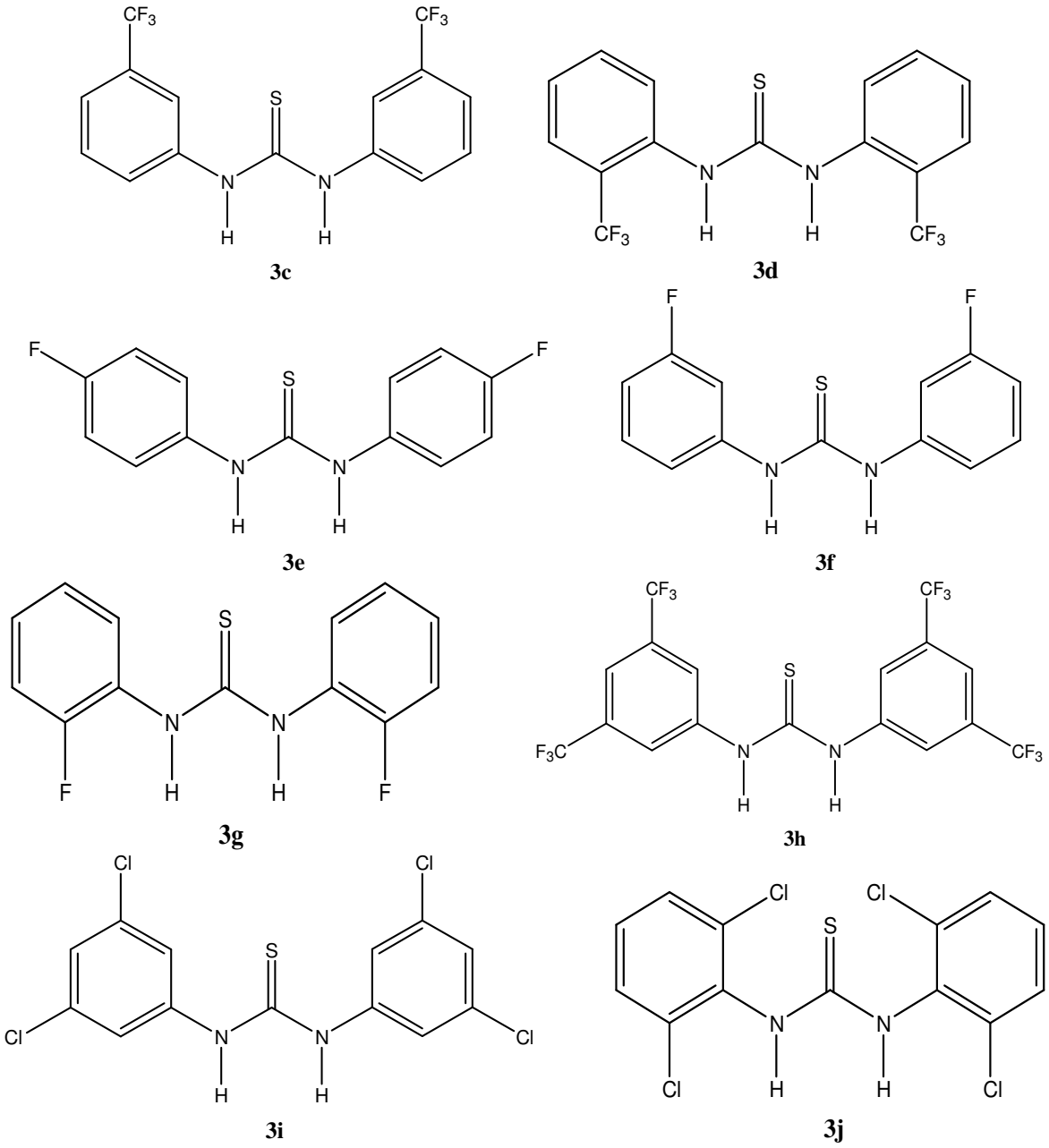
Scheme 2: The reaction between α,β-unsaturated aldehydes/ketones to cyclopentadiene in the presence of N,N'-disubstituted thiourea derivative as promoter.

In 2003, catalytic effectiveness of a series of symmetrically substituted thiourea was investigated by Schreiner and co-workers.[8,9] Results showed that the catalyst with electron withdrawing group i.e., CF_3 moiety posses great catalytic behavior with high yield.

Subsequently, a large number of the thiourea based catalysts were developed[9]; structures of afew are shown below.



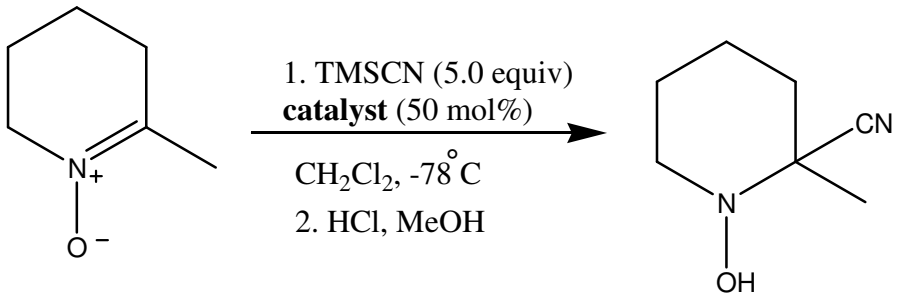
3a **3b**



Scheme 3: The symmetrically substituted thiourea used by Peter R. Schreiner.[9]

A comparative study was done by Takemoto and his co-workers on a chemical reaction on the basis of the position of the CF_3 moiety and results showed that catalyst **3** was most effective.[13]

Furthermore, the catalytic activities of the three catalysts, 4a, 4b and 4h were compared.[9]



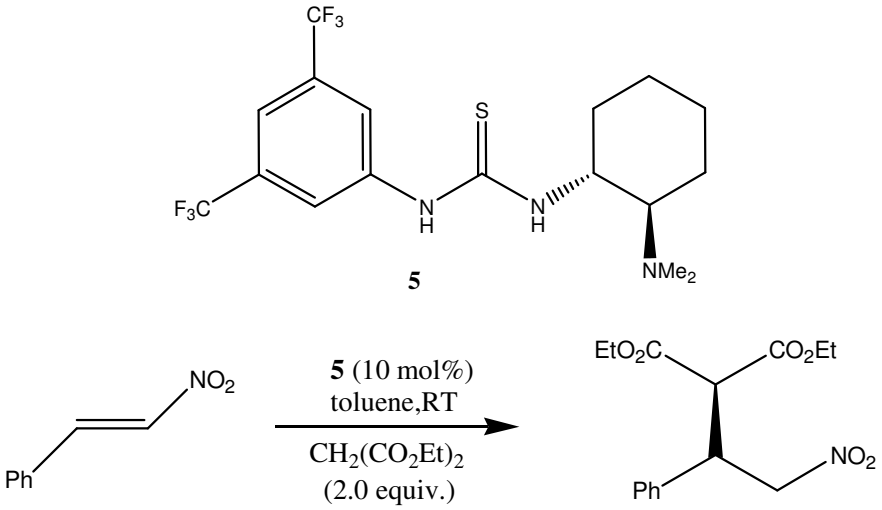
catalyst	t [h]	yield [%]
none	300	75
4a	45	81
4b	15	75
4h	15	81

Scheme 4: Addition of TMSCN to nitrones catalysed by thiourea catalysts.

BIFUNCTIONAL THIOUREA DERIVATIVES:

Bifunctional catalysis concerns the use of low molecular weight, structurally defined molecules possessing two distinct functional groups to bring about new reactivity or selectivity in a reaction. Many bifunctional catalysts possess either Lewis or Bronsted basic functionality and a hydrogen bond donor group suitably positioned over a chiral scaffold. Comparatively, the cooperative effect of the two complimentary functional groups can lead to new reactivity and stereoselectivity is more.[14]

The first thiourea based bifunctional catalyst reported was tertiary amine (Scheme 5), which was capable of the efficient promotion of the addition of malonate esters to β'-nitrostyrenes with excellent enantioselectivity.[13]



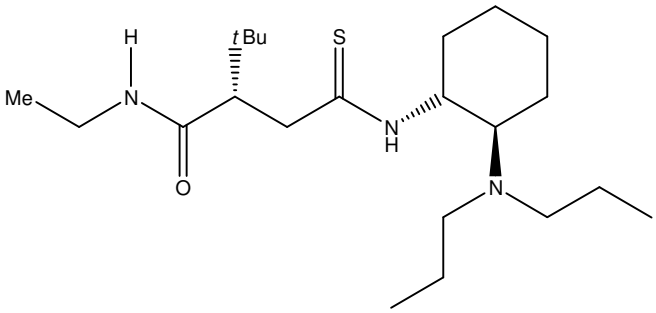
Scheme 5: Takemoto's thiourea-amine catalysis.

Takemoto[13] demonstrated that chiral bifunctional organic catalysts **5** containing thiourea and tertiary amino groups effectively activated nitro compounds for enantioselective Aza-Henry and Michael reactions.[13]

Berkessel et al. have successfully applied **5** and its urea derivative to the dynamic kinetic resolution (DKR) of racemic azalactone.[15]

In 2005, Hedrick et al. have expanded the scope bifunctional organocatalysis to include polymerization reactions. The use of catalyst **5** was found to initiate the living polymerization of lactide with minimal competing transesterification was observed.[14]

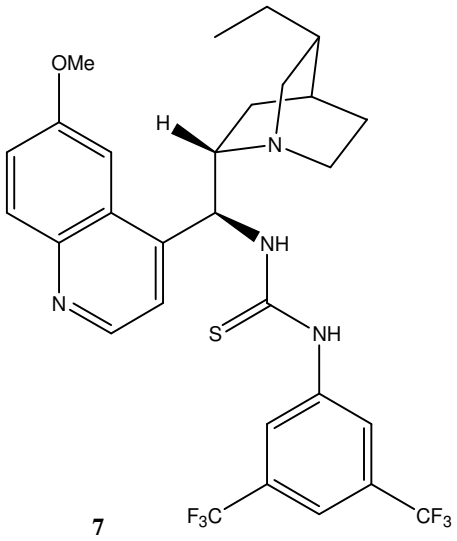
In 2005, Jacobsen and co-workers modified the structural backbone of catalyst **2** to incorporate tertiary amino functionality.[16] Thiourea **6** was demonstrated to be optimal for the highly efficient and selective for cyanosilylation of ketones.



6

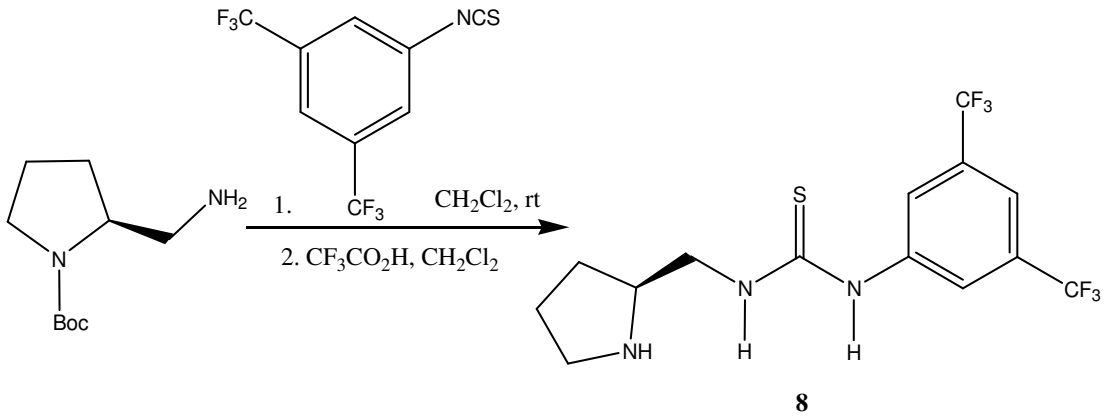
Jacobsen[17]exploited a variety of urea and thiourea based catalysts for Strecker, Mannich, Pictet – Spengler, and hydrophosphonylation reactions. These catalysts were proposed to activate a variety of carbonyl and sulphoxide substrates for stereoselective C-C bond forming reaction.[14]

In 2005, Soós et al. and Cannon have investigated the use of the thiourea substituted cinchona alkaloid **7** derivatives as bifunctional catalysts.[18]



7

In 2007, Dolman and Wong reported the incorporation of chiral scaffold.



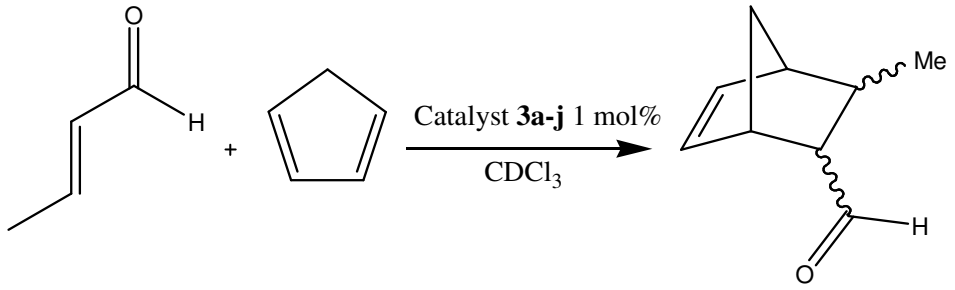
8

Scheme 6: Synthesis of chiral thiourea based organocatalyst.[19]

Application of thiourea based organocatalyst:

The application of some thiourea based catalysts for a few reactions is outlined below.

Diels-Alder reaction:

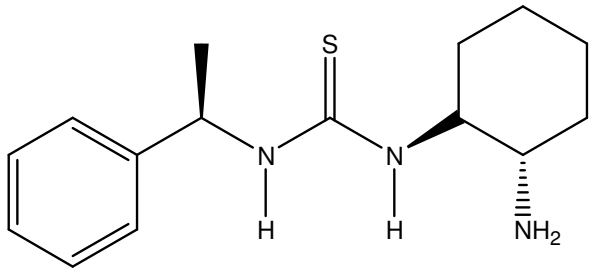


Scheme 7: Diels-Alder reaction of α,β-unsaturated carbonyls with cyclopentadiene.[9]

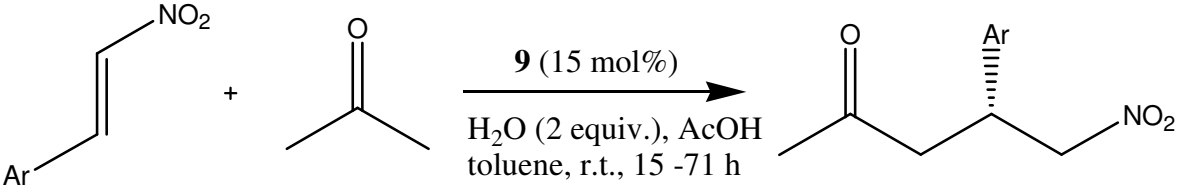
Schreiner and co-workers investigated the catalytic effect of a series of symmetrically substituted thioureas **3a-j**.

Michael addition:

In 2006, Tsogoeva and co-workers introduced bifunctional organocatalyst **9**, bearing both thiourea moiety and primary amine group on a chiral scaffold. On reacting acetone with aromatic nitroolefins gives the product γ-nitro ketones in a good yield (85.5-93%) and enantioselectivity (84-92% ee) (Scheme 8).[20,21]

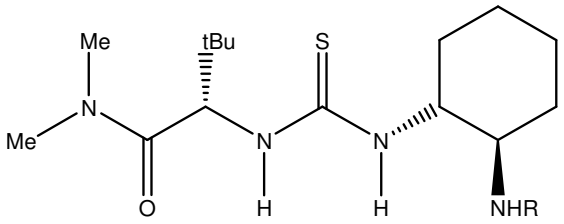


9



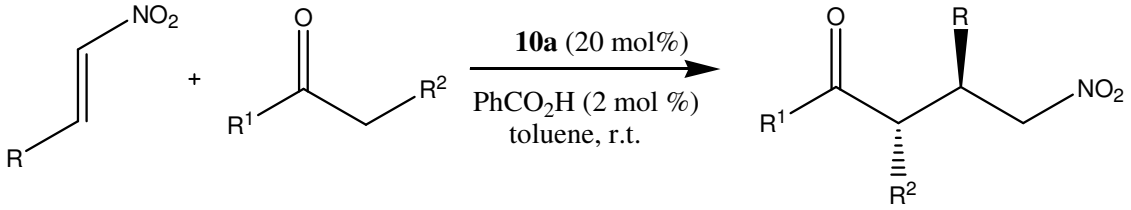
Scheme 8: Using bifunctional derivative

In 2006, the use of another primary amine-thiourea organocatalyst **10** was reported for Michael addition of ketones to nitroolefins.[22]



10

10a = H
10b = Ac



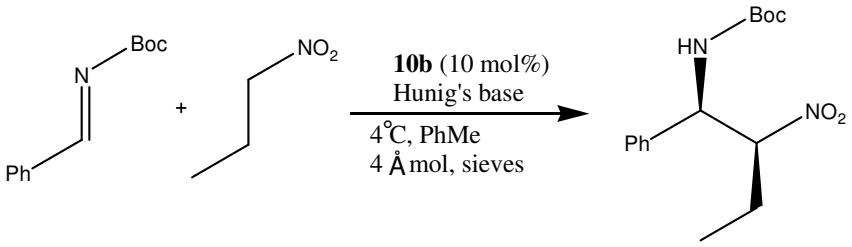
R = Me, n-Bu, *i*-Bu, Ar
R^1= Me, Et, n-Pr, n-Bu, *i*-Bu, n-pentyl
R^2= H, Me, OMe

50-94% yields

Scheme 9: Michael addition reaction using thiourea derivative.[22]

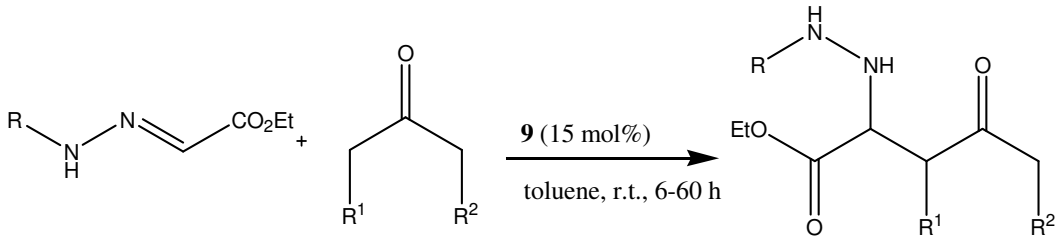
Mannich reactions:

Interestingly, it has found that simplification of catalyst **2** is possible without any loss of enantioselectivity.



Scheme 10: Nitro-Mannich reaction.[23]

In 2008, Tsogoeva and co-workers reported that bifunctional primary amine derived chiral thiourea **9** could successfully catalyze the asymmetric Mannich-type reaction of unmodified ketones with readily available and stable α-hydrazonoesters.[24]



R = Bz, 4-MeOBz, 4-BrBz, 4-NO_2Bz
R^1 = H, Me, Et, -$(CH_2)_3$
R^2 = H, Et, n-Pr, *i*-Pr, cyclohexyl

45-89% yields

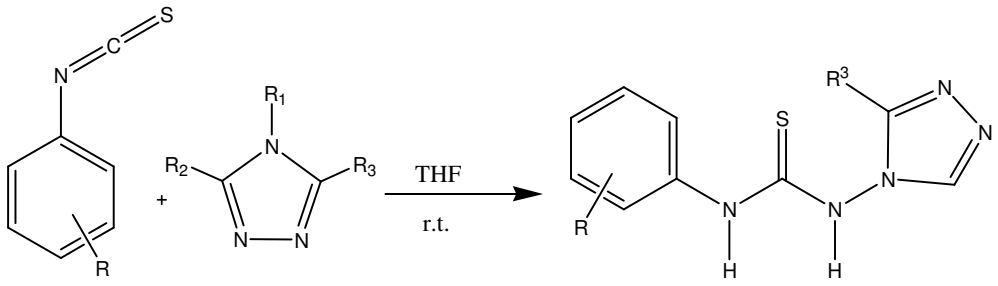
Scheme 11:Asymmetric Mannich reaction using chiral catalyst.

Proposed work:

Survey of literature showed that the bifunctional thiourea derivatives having the triazole moiety have not been reported so far. It is therefore proposed to synthesis a few thiourea based organocatalyst having 1,2,4-triazole moiety.

1. **Synthesis of new thiourea based organocatalysts**
   a) **Synthesis of triazole based thiourea organocatalyst:**

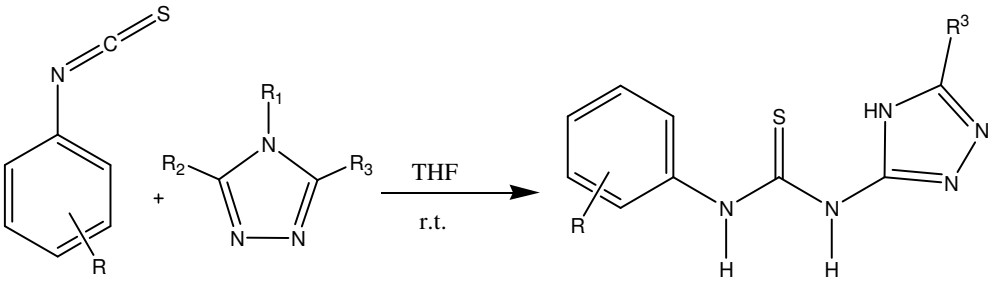
      By using 4-amino triazole



R= H, CF_3, NO_2, F.

REACTANT	R_1	R_2	R_3
A	NH_2	H	H
B	NH_2	H	2-pyridyl
C	NH_2	SH	4-pyridyl

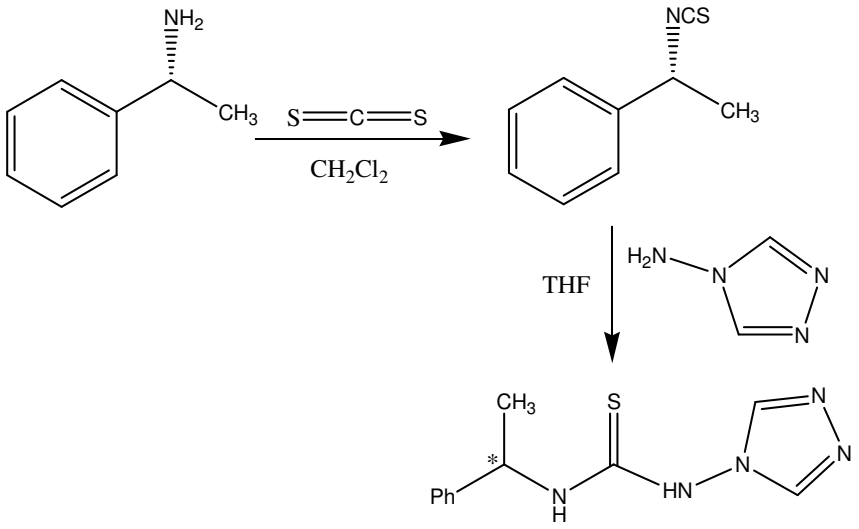
b) Synthesis by using 3-amino triazole:



R= H, CF_3, NO_2, F.

REACTANT	R_1	R_2	R_3
A	H	NH_2	H
B	H	NH_2	SH

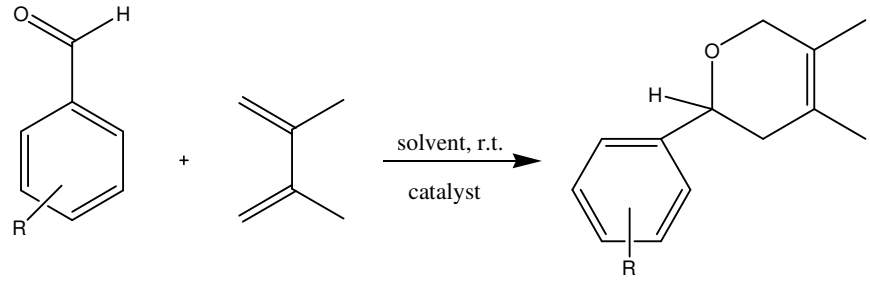
c) **Synthesis of chiral catalyst :**



On reacting (R)-(+)-α-methylbenzylamine with CS_2 in the presence of methylene chloride leads to formation of isothiocyanate derivative,which will further be used for synthesis of chiral catalyst.

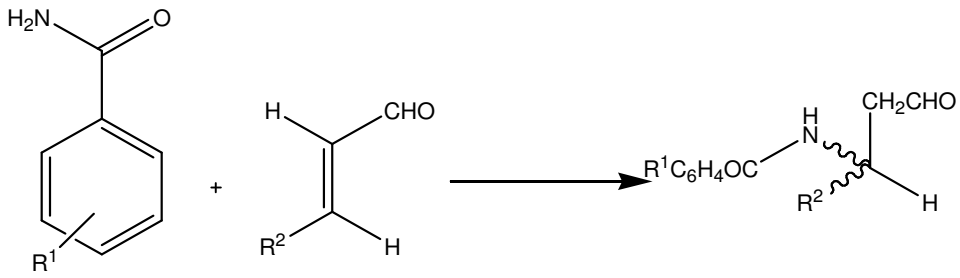
2. Application of the catalyst for accomplishing organic reactions:

a) Oxa-Diels-Alder reaction using above catalyst:



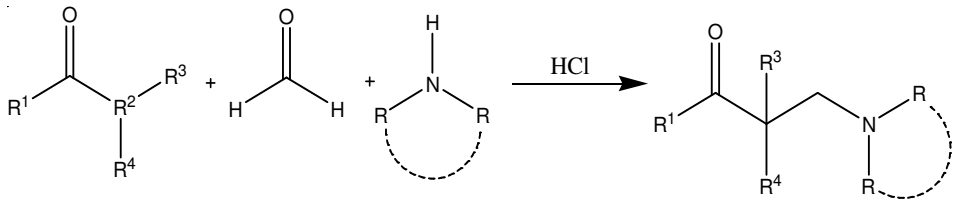
R = *p*-NO_2, *p*-Br, *p*-OH

b) Michael addition of amides:



R^1 = H, Me, OMe, NO_2
R^2 = Me, Ph

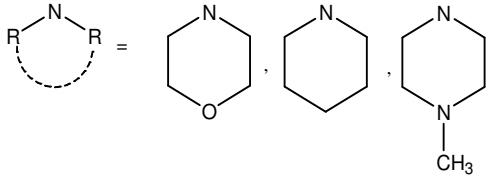
c) Mannich reaction:



R^1 = H, Me

R = $-CH_2CH_3$

	R^2	R^3	R^4
a	CH	H	H
b	CH	H	CH_3
c	CCH_3	CH_3	CH_3



d) **Asymmetric reactions using chiral catalysts:**

In the above reactions, chiral catalyst will be used and enantioselectivity will be determined

Methodology:-

We have already carried out a reaction, using the given method. The other reactions will be carried out analogously by varying reaction conditions. To a solution of *p*-nitrobenzaldehyde (0.5 mmol, 75 mg) in CH_2Cl_2 (10 mL) taken in a 100 mL R.B flask was added the catalyst at r.t., After stirring the reaction mixture for 30 min. at r.t. (~25˚C) was added DMB (2 fold excess, 1 mmol, 82 mg, 0.15mL) and the reaction mixture stirred at r.t for 24 hr, progress of the reaction being monitored by TLC. After completion of reaction, reaction mixture was concentrated to 2-3 mL.

The crude product was purified by column chromatography over silica gel, compound was obtained.

Characterization of the products**.** The products will be characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, 2D-NMR and by HRMS**.**

Facilities available at the place of work

- A well equipped research laboratory
- As we do not have facilities for the element analysis and spectral studies at the IIS university , the same will be availed at the local Malaviya National Institute of technology and Thera Chem on payment basis.

References :

1. S. J. Connon, *Chem. Commun.***2008**, 2499-2510.
2. F. G. Bordwell, D. J. Algrim, J. A. Harrelson, *J. Am. Chem. Soc.***1988**, 100, 5903.
3. D. P. Curran, L. H. Kuo, *J. Org. Chem.***1994**, 59, 3259-3261.
4. D. P. Curran, L. H. Kuo, *Tetrahedron Lett.***1995**, 36, 6647-6650.
5. A. G. Doyle, E. N. Jacobsen, *Chem. Rev.***2007**, 107, 5713.
6. Y.-L Sun, Y. Wei, M. Shi, *Chem. Cat. Chem.***2017**, 9(5), 718-727.
7. A direct comparison between the performance of catalyst 3 and its urea derivative was studied on Claisen rearrangement.
8. P. R. Schreiner, A. Wittkopp, *Org Lett.***2002**, 4, 217.
9. P. R. Schreiner, A. Wittkopp, *Chem. Eur. J.* **2003**, 9, 407.
10. K. A. Haushalter, J. Lau, J. D. Roberts,*J. Am. Chem. Soc.***1996**, 118, 8891.
11. M. S. Sigman, E.N. Jacobsen, *J. Am. Chem. Soc.***1998**, 120, 4901.
12. S. J. Connon, *Chem. Eur. J.***2006**, 12, 5418-5427.
13. T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.***2003**, 125, 12672.
14. A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.***2005**, 127, 13798-13799.
15. A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Muller, *J. Lex. Angew. Chem.***2005**, 117, 817.
16. D.E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.***2005**, 127, 8964.
17. M. S. Sigman, E. N. Jacobsen, *Chem. Int. Ed.***2000**, 39, 1279.
18. B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.***2005**, 7, 1967.
19. R. Wong, S. J. Dolman, *J. Org. Chem.***2007**, 72, 3969.
20. S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451.
21. D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, 348, 826.
22. H. Haung, E. N. Jacobsen, *J. Am. Chem. Soc.***2006**, 128, 7170.
23. M. S. Taylor, N. Torunaga, E. N. Jacobsen, *Angrew. Chem.***2005**, 117, 6858.
24. D. A. Yalalov, S. B. Tsogoeva, T. E. shubina, I. M. Martynova, T. Clark, *Angrew. Chem. Int. Ed.* **2008**, 47, 6624.